SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluticasone propionate Alissa 50 microgram/actuation nasal spray, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 50 micrograms of fluticasone propionate per dose.

Excipients with known effect: benzalkonium chloride.

Contains 20 microgram of benzalkonium chloride per dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, suspension

White opaque suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis.

Fluticasone propionate Alissa is indicated in adults and adolescents aged 12 years and older and in children aged 4 to 12 years.

4.2 Posology and method of administration

Fluticasone propionate Alissa is for intranasal use only.
Avoid eye contact.

Posology

Adults and adolescents (aged 12 years and older)

The recommended dose is two sprays into each nostril once a day, preferably in the morning. In some cases two sprays into each nostril twice daily may be required. The maximum daily dose is four sprays per nostril.

Paediatric population
Children aged 4 to 12 years
The recommended dose is one spray into each nostril once a day, preferably in the morning. In some cases one spray into each nostril twice daily may be required. The maximum daily dose is two sprays per nostril.

Children under 4 years of age
Fluticasone propionate Alissa should not be used in children aged under 4 years because safety and efficacy have not been established.

Elderly population
The normal adult dosage is applicable.

For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient, as maximum relief may not be obtained until after 3 to 4 days of treatment.

Method of administration

Shake before use.

When using a new bottle, prepare it by pumping 5 times in the air.
If the bottle has not been used for a week, it should be prepared by pumping once.

To use the spray, place the nozzle in one nostril whilst the other is closed, ensuring the nozzle is aimed away from the nasal septum. Spray into the nostril whilst breathing in and then breathe out through the mouth.

After usage, the nose piece and inside of the protector cap should be cleaned with a dry and clean tissue. Once a week the protection cap and the actuator need to be cleaned with water, by immersing them in lukewarm water and leaving to dry at room temperature. The actuator should not be removed.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Maximum relief may not be obtained until after 3 to 4 days of treatment.

Local infections: infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with intranasal fluticasone propionate.

Although Fluticasone propionate Alissa will control seasonal allergic rhinitis in most cases, an abnormally heavy challenge of summer allergens may in certain instances necessitate appropriate additional therapy.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for doses higher than recommended being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery (see Section 5.1 for data on intranasal fluticasone propionate).

During post-marketing use, clinically significant drug interactions were described in patients using both fluticasone propionate and ritonavir. Concomitant use resulted in systemic corticosteroid side effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see section 4.5).
effects may include Cushing's syndrome, Cushingoid features, adrenal suppression and more rarely, cataract, glaucoma, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (especially in children).
Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses (see paediatric information).

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Fluticasone propionate Alissa contains 20 microgram of benzalkonium chloride per dose. Long-term use may cause oedema of the nasal mucosa.

Paediatric population

Potential systemic effects may include growth retardation in adolescents and depression or aggression.

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored (e.g. via stadiometry). If there is any suspicion of slow growth, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

Co-treatment with other potent CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side effects. Concomitant use should be avoided unless the potential benefit to the patient outweighs the increased risk of systemic corticosteroid side effects, in which case patients have to be monitored for systemic corticosteroid side effects.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. significantly increased the fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use clinically significant drug interactions were observed in patients using both intranasal or inhaled fluticasone propionate and ritonavir. Concomitant use resulted in systemic corticosteroid side effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use should be avoided, unless the benefit outweighs the risk of systemic corticosteroid side effects (see section 4.4 and 5.2).

Other inhibitors of CYP3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects.

	Fluticasone		Cortisol
Treatment	C_{max} (pg/ml)	AUC_{0-t} (pg.u/ml)	Ratio AUC_{24} (treatment/placebo
Fluticasone (200 µg intranasal)	12	8	1.03 (90% BI 0.82 – 1.29)
+ erythromycin (500 mg bid)	15	55	0.98 (90% BI 0.80 – 1.20)
+ ketoconazole (200 mg qd)	44	162	0.93 (90% BI 0.75 – 1.14)
+ ritanovir (100 mg bid)	318	3103	0.14 (90% BI 0.11 – 0.18)

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of fluticasone propionate in pregnant women. Animal studies have shown fluticasone propionate to cause congenital malformations (see section 5.3). However, systemic concentrations of fluticasone after inhalation are very low and the placenta is a rich source of enzymes that can metabolize corticosteroids. Therefore, clinically significant exposure of the embryo or foetus is unlikely.

As a precautionary measure, it is preferable to avoid the use of Fluticasone propionate Alissa during pregnancy.

Lactation

It is unknown whether fluticasone propionate/metabolites are excreted in human milk. Subcutaneous administration of fluticasone propionate to rats produced measurable plasma levels and evidence of fluticasone propionate in the milk. However, following intranasal administration, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to fluticasone propionate is negligible.

Fluticasone propionate can be used during breast feeding.

Fertility

There is no information available on the effect of fluticasone propionate on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Fluticasone propionate Alissa has no or negligible influence on the ability to drive and use machines.

Visual disturbances have been reported with intranasal fluticasone propionate. Patients presenting with blurred vision or other visual disturbances should be warned to avoid activities such a driving and using machines.

4.8 Undesirable effects

The most common side effect experienced after administration is epistaxis; however most cases are non-serious in nature and self-limiting. The most serious events are anaphylactic/anaphylactoid reactions, bronchospasm and nasal septal perforation.

Very common and common events were generally determined from clinical trial data. Very rare events were generally determined from spontaneous post-marketing data. In assigning adverse event frequencies, the background rates in placebo groups were not taken into account.
Adverse events are listed below by system organ class and classified according to the following frequencies:

Very common ≥1/10
Common ≥1/100, <1/10
Very rare <1/10.000
Not known frequency cannot be estimated from the available data

System organ class	**Very common**	**Common**	**Very rare**	**Unknown**
Immune system disorders			Hypersensitivity reactions, anaphylactic/ anaphylactoid reactions, bronchospasm, skin rash, oedema of the face and tongue	
Nervous system disorders		Headache, unpleasant taste, unpleasant smell		
Eye disorders			*Glaucoma, intraocular pressure, cataract	Vision blurred (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Epistaxis	Nasal dryness, nasal irritation, throat dryness, throat irritation	Nasal septum perforation**	Nasal ulcer

* *Adverse events following long-term treatment spontaneously collected in post-marketing experience.*
** *Class effect: reported following the use of intranasal corticosteroids.*

Systemic effects of some nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods (see section 4.4).

Paediatric population

Systemic effects of some nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods (see section 4.4).

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

There are no data available on the effects of acute or chronic overdosage with intranasal fluticasone propionate. Intranasal administration of 2 mg fluticasone propionate twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nasal preparations, corticosteroids, ATC code: R01AD08

Mechanism of action

Fluticasone propionate has potent anti-inflammatory activity, but systemic activity was not quantifiable when administered intranasally.

Pharmacodynamic effects

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal or topical (dermal) administration.

Following intranasal dosing of fluticasone propionate (200 micrograms/day), no significant change in 24 hour serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14).

Paediatric population

In a 1-year randomised, double-blind, placebo-controlled, parallel group growth study in pre-pubescent children aged 3 to 9 years (56 patients receiving intranasal fluticasone propionate and 52 receiving placebo,) no statistically significant difference in growth velocity was observed in patients receiving intranasal fluticasone propionate (200 micrograms per day nasal spray) compared to placebo. The estimated growth velocity over one year of treatment was 6.20 cm/year (SE=0.23) in the placebo group and 5.99 cm/year (SE=0.23) in the fluticasone propionate group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% CI= -0.35, 0.76). No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

5.2 Pharmacokinetic properties

Absorption

Following intranasal dosing of fluticasone propionate (200 micrograms/day), steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01 ng/mL). The highest Cmax observed was 0.017 ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Distribution

Fluticasone propionate has a large volume of distribution at steady-state (approximately 318 L). Plasma protein binding is moderately high (91%).

Biotransformation

Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate.

Elimination

The elimination rate of intravenous administered fluticasone propionate is linear over the 250-1000 micrograms dose range and are characterized by a high plasma

clearance (CL=1.1 L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites

5.3 Preclinical safety data

Toxicology studies in animals, including reproductive and development toxicology studies, have shown class effects typical of a potent corticosteroid, and these only at doses greatly in excess of those proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests.

Fluticasone propionate is devoid of mutagenic activity in vitro and in vivo and showed no tumorigenic potential in rodents. It is both non-irritating and non-sensitising in animal models.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Glucose

Microcrystalline cellulose (E460i) and carmellose sodium (E466)

Phenylethyl alcohol

Polysorbate 80

Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 30 months

Opened bottle: 3 months

6.4 Special precautions for storage

Store upright.

6.5 Nature and contents of container

White PP bottle with a PE/PP/EVA spray pump. Pack sizes of 60, 120 or 150 actuations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alissa Healthcare Research Ltd.

Unit 5, Fulcrum 1

Whiteley, Fareham

Hampshire PO15 7FE

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30322/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/09/2021

10 DATE OF REVISION OF THE TEXT

09/11/2021